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CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
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ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,

[Continued on next page]

(54) Title: METHODS AND AGENTS FOR DIAGNOSIS AND PREVENTION, AMELIORATION OR TREATMENT OF GOB-
LET CELL-RELATED DISORDERS

BLAST 2 Sequences

(<http://www.ncbi.nlm.nih.gov/blast/bl2seq/bl2.html>)

Sequence 1: mouse AGR2 (WT); SEQ ID No:3
Sequence 2: human AGR2 (WT); SEQ ID No:4

NOTE: The statistics (bitscore and expect value) is calculated based on the
size of nr database.

Score = 323 bits (828), Expect = 4e-88
Identities = 160/175 (91%), Positives = 168/175 (95%)

Query: 1 MEKFSVSAILLVVAISGTLAKDITTVKSGAKKDPKDSRPKLPQTLSRGWGDQLIWTQTYEE 60
MEK VSA LLLVA+S TLA+DTTVK GAKKD KDSRPKLPQTLSRGWGDQLIWTQTYEE
Sbjct: 1 MEKIPVSAFLLVVAISYTLARDITTVKPGAKKDKDSRPKLPQTLSRGWGDQLIWTQTYEE 60

Query: 61 ALYRSKTSNRPLMVIHHLDECPHSQALKKVFVAENKEIQKLAEQFVLLNLVYETTDKHLSP 120
ALY+SKTSN+PLM+IHHLDECPHSQALKKVFVAE+KEIQKLAEQFVLLNLVYETTDKHLSP
Sbjct: 61 ALYKSKTSNKLPMIHHLDECPHSQALKKVFVAENKEIQKLAEQFVLLNLVYETTDKHLSP 120

Query: 121 DGQYVPRI+VFDPSLT+RADITGRYSNRLYAYEP+DTALL DNMMKALKLKTTEL 175
DGQYVPRI+VFDPSLT+RADITGRYSNRLYAYEP+DTALL DNMMKALKLKTTEL
Sbjct: 121 DGQYVPRI+VFDPSLT+RADITGRYSNRLYAYEP+DTALL DNMMKALKLKTTEL 175

(57) Abstract: The present invention is based on the observation that hAG-2 or gob-4 (homologue of the xenopus laevis cement gland gene XAG-2, also called herein AGR2) is required for normal goblet cell function in particular mucus production. In particular, one mutant with impaired mucus production was isolated. It carries an amino acid exchange valine to glutamic acid at position 137. A transgenic mouse carrying this mutation shows diarrhea and thriving deficit. Based on this observation the present invention relates inter alia to products and methods for the prevention, amelioration or treatment of medical conditions associated with an alteration in normal goblet cell function.

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SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Declaration under Rule 4.17:

— as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR,

Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14834

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/47 C12N15/12 C12N15/62 C12N5/10 C07K16/18
G01N33/53 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, SEQUENCE SEARCH, SCISEARCH, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98/41627 A (ZYMOGENETICS INC) 24 September 1998 (1998-09-24) SEQ ID's 1 and 2 page 23 -page 26 ---	45-48, 50-53, 69,71, 104-126, 135-153, 183-186, 188-190, 192-196, 200-205 -/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

3 June 2004

Date of mailing of the international search report

22/06/2004

Name and mailing address of the ISA

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Steffen, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/14834

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/63290 A (BOYD ROBERT SIMON ;OXFORD GLYCOSCIENCES UK LTD (GB); STAMPS ALASDA) 30 August 2001 (2001-08-30) page 6 -page 8; figure 1; examples 1,2	45-48, 50-53, 69,71, 104-126, 135-153, 183-186, 188-190, 192-196, 200-205
Y	KOMIYA T ET AL: "Cloning of the gene gob-4, which is expressed in intestinal goblet cells in mice." BIOCHIMICA ET BIOPHYSICA ACTA. NETHERLANDS 19 MAR 1999, vol. 1444, no. 3, 19 March 1999 (1999-03-19), pages 434-438, XP002283077 ISSN: 0006-3002 page 436 -page 438; figures 1-3	45-48, 50-53, 69,71, 104-126, 135-153, 183-186, 188-190, 192-196, 200-205
Y	THOMPSON D A ET AL: "HAG-2, THE HUMAN HOMOLOGUE OF THE XENOPUS LAEVIS CEMENT GLAND GENE XAG-2, IS COEXPRESSED WITH ESTROGEN RECEPTOR IN BREAST CANCER CELL LINES" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 251, no. 1, 9 October 1998 (1998-10-09), pages 111-116, XP001009725 ISSN: 0006-291X page 114 -page 116; figures 1,3	45-48, 50-53, 69,71, 104-126, 135-153, 183-186, 188-190, 192-196, 200-205
A	GUPTA R A ET AL: "Target genes of peroxisome proliferator-activated receptor gamma in colorectal cancer cells." THE JOURNAL OF BIOLOGICAL CHEMISTRY. UNITED STATES 10 AUG 2001, vol. 276, no. 32, 10 August 2001 (2001-08-10), pages 29681-29687, XP002283078 ISSN: 0021-9258 page 29684; figure 4; table I	

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14834

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MONITTO C L ET AL: "Differential gene expression in a murine model of cancer cachexia." AMERICAN JOURNAL OF PHYSIOLOGY. ENDOCRINOLOGY AND METABOLISM. UNITED STATES AUG 2001, vol. 281, no. 2, August 2001 (2001-08), pages E289-E297, XP002283079 ISSN: 0193-1849 page E294 -page E295; table 3</p>	
A	<p>YAGUI-BELTRAN A ET AL: "The human oesophageal squamous epithelium exhibits a novel type of heat shock protein response." EUROPEAN JOURNAL OF BIOCHEMISTRY / FEBS. GERMANY OCT 2001, vol. 268, no. 20, October 2001 (2001-10), pages 5343-5355, XP002283080 ISSN: 0014-2956 page 5352, right-hand column, paragraph 2; figure 9</p>	
A	<p>PETEK E ET AL: "LOCALIZATION OF THE HUMAN ANTERIOR GRADIENT-2 GENE (AGR2) TO CHROMOSOME BAND 7P21.3 BY RADIATION HYBRID MAPPING AND FLUORESCENCE IN SITU HYBRIDISATION" CYTOGENETICS AND CELL GENETICS, BASEL, CH, vol. 89, no. 3/4, 2000, pages 141-142, XP008028946 ISSN: 0301-0171 the whole document</p>	
A	<p>ABERGER F ET AL: "ANTERIOR SPECIFICATION OF EMBRYONIC ECTODERM: THE ROLE OF THE XENOPUS CEMENT GLAND-SPECIFIC GENE XAG-2" MECHANISMS OF DEVELOPMENT, ELSEVIER SCIENCE IRELAND LTD, IE, vol. 72, no. 1/2, March 1998 (1998-03), pages 115-130, XP001189066 ISSN: 0925-4773 the whole document</p>	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/14834

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 96-103 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 172-182, 184-186, 190 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 36, 41, 45, 49, 69, 71, 73, 104, 105 (partly); 184, 187, 190 (partly), 191, 206, 207

Claims 36, 41, 45, 49, 69, 71, 73, 104, 105 (partly) relate to a structurally non-defined gene encoding a protein or a structurally non-defined corresponding protein which is defined by a parameter or property, namely the ability to affect expression of function of the Agr2 protein. Such gene or protein is not revealed in the present application however. The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, no search has been carried out for those parts of claims 36, 41, 45, 49, 69, 71, 73, 104, 105, that relate to the above mentioned products.

Present claims 184, 187, 190 (partly), 191, 206, 207 relate to products defined by a parameter or property, namely the ability to modulate activity of the claimed molecules or to act either agonistically or antagonistically towards the claimed molecules or to have been identified by a method employing the claimed molecules. The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, no search has been carried out for claims 184, 187, 191, 206, 207 and for those parts of claim 190, that relate to the above mentioned products.

Moreover, the claims cover all products having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search is impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/14834

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9841627	A	24-09-1998	AU 6762298 A WO 9841627 A1	12-10-1998 24-09-1998
WO 0163290	A	30-08-2001	AU 3391201 A AU 3391301 A AU 3391701 A AU 3392901 A AU 3576101 A BR 0108659 A CA 2399999 A1 CN 1426307 T EP 1259604 A1 EP 1259814 A1 EP 1257285 A2 EP 1257827 A1 WO 0163288 A1 WO 0162914 A1 WO 0163289 A1 WO 0163290 A1 WO 0162784 A2 JP 2003524017 T US 2003099662 A1 US 2004053830 A1 US 2003130214 A1 US 2002111303 A1 US 2003017456 A1	03-09-2001 03-09-2001 03-09-2001 03-09-2001 03-09-2001 05-11-2002 30-08-2001 25-06-2003 27-11-2002 27-11-2002 20-11-2002 20-11-2002 30-08-2001 30-08-2001 30-08-2001 30-08-2001 30-08-2001 12-08-2003 29-05-2003 18-03-2004 10-07-2003 15-08-2002 23-01-2003